Key Issues and Perspectives for Drug Metabolism and Pharmacokinetics in Drug Discovery and Development

Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Kimihiko Sato
Takao Watanabe
Kazuhiko Nishioka
Masashi Yabuki
Setsuko Komuro

Recently pharmacokinetics is increasingly gaining weight in the development of new drugs. At every stage of the development process (from discovery to sales and even after the launch of a product), it is becoming essential to generate appropriate pharmacokinetics information in a timely manner. The information is quite useful and, therefore, enables us to make a go/no-go decision on a sound scientific basis. This report presents an overall picture of pharmacokinetics study conducted at our laboratory including some methods employed for this purpose. In addition, one of the new technologies that are expected to empower the pharmacokinetics study as well as clinical trials is described.

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Introduction

On average, the successful commercialization of one new drug requires the initial assessment of more than 10,000 different chemical compounds. Of all these 10,000 or more compounds, somewhere between several hundred and several thousand of them must actually be synthesized. Among the compounds synthesized, perhaps only one hundred or so will actually pass screening tests. The screened compounds are subsequently subjected to a detailed experimental regimen, including animal testing, which reduces the list to a mere dozen or so substances that have potential in effective new drug applications. Clinical trial and other procedures are then conducted on these candidate substances, until finally the new drug is ready for market introduction. The development period for new drugs generally ranges from 8 - 15 years, with research and development costs in the tens of billions of yen. Furthermore, these figures have been increasing year by year.

The annual global market for pharmaceuticals is worth approximately 49 trillion yen (2003). Japan's share of this market is valued at approximately 7.1 trillion yen (2003) and has been undergoing steady growth. For example, the drug "Lipitor" (a cholesterol-lowering medication manufactured by Pfizer Inc.) was the top-selling drug during 2003, with sales of 10.1 billion dollars (approximately 1.111 trillion yen). In second place was "Zocor" (a cholesterol-lowering medication manufactured by Merck & Co., Inc.) with sales of 6.1 billion dollars (approximately 671 billion yen) and in third place was "Zyprexa" (an antipsychotic drug manufactured by Eli Lilly & Company) with sales of 4.8 billion dollars (approximately 528 billion yen).

In the midst of intense pharmaceuticals competition, which is aimed at the development of "blockbuster" drugs, up until recently one of the primary reasons that pharmaceutical companies have withdrawn drugs during development process, had been due to poor pharmacokinetics profile of their candidate chemical compounds (**Fig. 1**). In other words, almost 40% of all cases of interrupted or withdrawn drug development occurred due to unacceptable pharmacokinetics relating to either drug absorption, distribution, metabolism or excretion. Furthermore, poor drug efficacy and the manifestation of undesirable side effects were also derived from unacceptable pharmacokinetics profile, thus revealing that pharmacokinetics was at the root of almost 80% of all instances of failed drug development efforts. In order to solve these problems, pharmaceutical companies have been conducting vigorous pharma-

cokinetics research, beginning from the earliest stages of drug development. As a result of this comprehensive body of research, it has recently been reported that the number of failed drug development efforts due to poor pharmacokinetics profile has decreased tremendously.

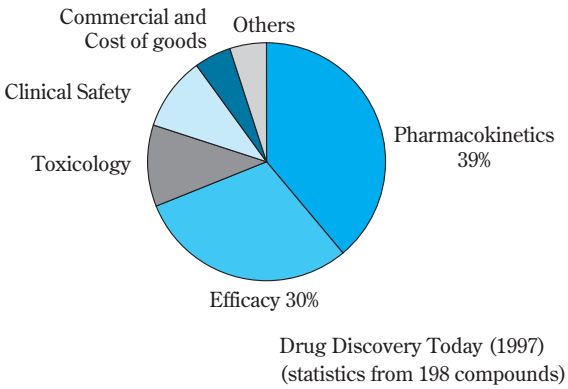


Fig. 1 Reasons for withdrawal from clinical trial 7-8 years ago

The ultimate goal of pharmacokinetics research is to predict "the kind of chemical behavior that is demonstrated after the administration of a drug into man." For actual research procedures, in addition to classical animal study (*in vivo* testing using rats, mice, dogs and monkeys), *in vitro* testing has recently become more popular, utilizing samples originated from humans (tissues, cells and cell components), in order to help clear the hurdles associated with differences between species. Furthermore, significant advances have also been made in prediction technology using computer modeling (*in silico*).

Our group conducts comprehensive research into drug pharmacokinetics, beginning right from the selection of initial candidate compounds, through the development stages, to the approval process, even continuing after market launch. This paper describes the progress of each stage of our pharmacokinetics research, including the challenges facing us at each stage.

Pharmacokinetics Problems and Solutions

1. Pharmacokinetics at the Investigative Stage

Among the various pharmacokinetics problems that may result in the discontinuation of drug development, the most important problems are as follows: (i) after administration in the human body, the plasma concentrations of drug are too low and/or the half-life is too short; (ii) drug-drug interactions, which result in great fluctuations in the plasma concentrations of drug, causing either toxicity, or conversely, decreasing drug efficacy; and (iii) great difficulty in administering the appropriate dose of a drug to each patient, due to significant differences in drug reactions among individuals. Thus, when developing a new drug, it is crucial to evaluate these factors right at the earliest stages of development, in order to ensure that these problems can be avoided. Let us take a moment and consider what happens when we take a drug (oral tablet).

A tablet that is taken will disintegrate and become dispersed within the stomach (there are also certain drugs that are designed to disintegrate within the intestine, rather than in the stomach). After dispersion, the drug transfers to either the stomach or the small intestine, where it dissolves. The dissolved drug is thereby absorbed from the gastrointestinal tracts into the blood vessels (portal veins). Portal blood then flows to the liver, passing through it and transporting the drug into the systemic circulatory system, thus distributing the drug to the sites of action where its efficacy is demonstrated. Meanwhile, the drug is also metabolized within the liver or is excreted via the kidneys and thereby eliminated from the body (**Fig. 2**).

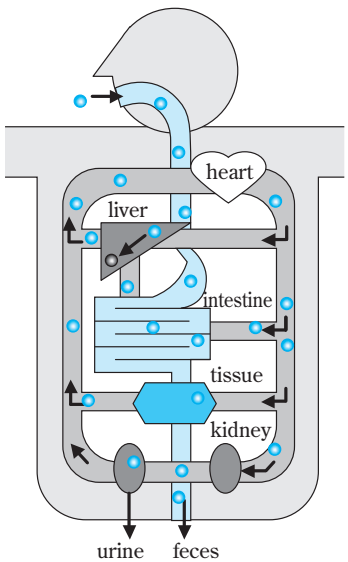


Fig. 2 Fate of drug in human

The above is a brief description of the phenomena that occur during the process of drug administration, until eventual elimination from the body. The three problems described previously are caused as follows:

(i) Inadequate plasma concentrations, insufficient half-life
  a) Insufficient absorption
  b) Rapid metabolism within the liver
(ii) Drug-drug interactions
  a) Inhibition of the drug metabolism in the liver
(iii) Significant differences among individuals
  a) Variances in the amount of drug absorption
  b) Individual differences in drug metabolism in the liver

Thus, it is apparent that a critical component of the drug development process is the evaluation of both drug absorption and metabolic properties, within the human body.

At the investigative stage, we focus specifically upon both absorption and metabolism as factors for pharmacokinetics evaluation, implemented in conjunction with drug efficacy screening. We are also engaged in establishing *in vitro* evaluation systems, in order to improve the speed of the evaluation process. Each of these evaluation methods is introduced below.

(1) Evaluation of Absorption (Membrane Permeability)

Unless a particular drug is actually administered to the body through clinical testing, it is impossible to know whether or not adequate absorption will occur. Therefore, during the investigative stage any reliable prediction of the body's drug absorbing ability will be extremely useful. Conventionally, chemical compounds being evaluated as potential drugs were selected using an index derived from the drug absorption ability in animal. However, the drug absorption in animal bodies does not necessarily equivalent to the same level of absorption within the human body. In order to predict the absorption of a drug into the human body, an *in vitro* evaluation system that uses Caco-2 cells is very useful (**Fig. 3**). Although Caco-2 cells are actually cancer cells derived from the human large intestine, they closely indicate the characteristics of the small intestine.

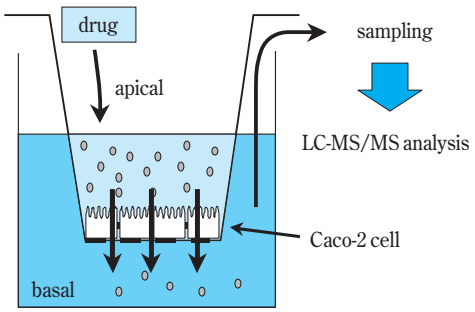


Fig. 3 Scheme of evaluation method of absorption potency using Caco-2 cell

After being cultivated on a 24-well plate for a period of 21 days, Caco-2 cells form microvilli, which are characteristic of the small intestine. This growth thus results in the formation of tight junctions between the cells, creating a single-layer polarized membrane. This membrane can now be used to evaluate drug absorption, through the following procedure: the drug is first added to the apical side of the single-layer membrane, comprised of cultivated Caco-2 cells. After a period of time, the amount of the drug that has permeated to the basal side of the membrane is measured, using LC-MS/MS, to obtain a permeability coefficient. A sigmoid-shaped correlation can be observed between the permeability coefficient obtained and the rate of absorption by the human body (**Fig. 4**). Thus, the absorption rate in humans can be predicted by adapting the permeability coefficient of the drug, for which the absorption rate is unknown, to a calibration curve that has been created from the evaluation results for known compounds.

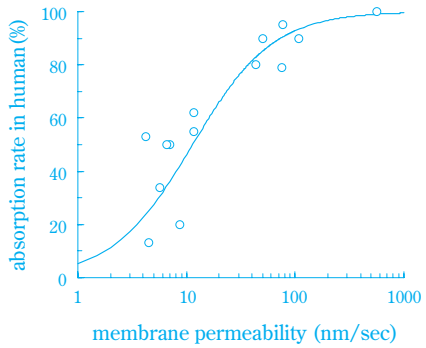


Fig. 4 Relationship between *in vitro* Caco-2 membrane permeability and human absorption rate

(2) Evaluation of Metabolic Stability

Absorbed drug must pass through the liver prior to entering the systemic circulation system. The degree of drug metabolism by the liver is a crucial factor that affect the net drug absorption, as only those compounds that are not fully metabolized by the liver after absorption will reach the systematic circulation system.

There are a number of known methods for evaluating the degree to which a compound is metabolized within the liver. Among these methods, a process that evaluates stability using hepatic S9 (a collection of frac-

tions containing metabolic enzymes from the liver) is most suitable for performing early stage evaluations that require the processing of many samples. The procedure is simple: a drug is added to the hepatic S9 solution and left to stand for a certain period of time. The amount of drug that remains unchanged is subsequently measured using LC-MS/MS. **Fig. 5** simulates the relationship between stability in human hepatic S9 and human liver availability (liver availability: "0" means that all of the drug is metabolized during passage through the liver; "1" means that none of the drug is metabolized during liver passage).

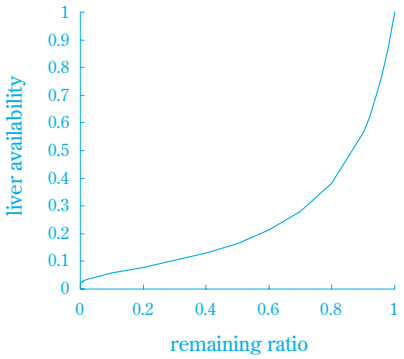


Fig. 5 Relationship between stability in human hepatic S9 (remaining ratio) and human liver availability

Although certain compounds may possess the same level of hepatic S9 stability, their liver availability may vary, depending upon other properties of the compounds, such as protein binding. Therefore, the simulation curve shown in this figure is that for a compound that is expected to have the minimum usable level of liver availability. For example, a compound that has a 50% remaining ratio after a certain period of enzymatic exposure is expected to have a liver availability that could exceed 15%. We would therefore place priority upon this type of compound for further evaluation.

Compounds that are to be subjected to further advanced evaluation using animal testing are usually selected by conducting the abovementioned *in vitro* tests during the primary screening stage, as well as by taking into account the results of pharmacological testing. These advanced evaluation procedures include: evaluation of changes in plasma concentrations of the compound when administered to experimental animals, such as rats, dogs or monkeys; elucidation of elimination routes for the compound (i.e., whether it is metabolized by the liver or excreted via the kidneys); identification of the metabolites produced; and identification of the enzymes associated with the metabolism of the compound. Through these high-stage evaluations, compound that possesses a comprehensive variety of favorable properties is selected as candidate.

However, it is important to understand that the obtained information in the investigative stage is limited because the experiments are conducted using non-radiolabeled compounds due to the difficulties in utilizing radiolabeled compound. The more detailed examinations, which do employ radiolabeled compound, are conducted later during developmental stage, after the selection of candidate compound.

2. Pharmacokinetics Research during the Drug Development Stage

Once candidate compounds have been selected and drug development initiated, a variety of safety tests are implemented to evaluate the safety of the compounds prior to clinical testing through administration to human subjects. These safety tests include *in vivo* toxicity testing using mammals (rats, dogs, monkeys, guinea pigs, etc.) and *in vitro* testing using cell cultures, such as genotoxicity study and safety pharmacology study. As well, radiolabeled compounds are then synthesized, in order to conduct the more precise testing needed for evaluating drug pharmacokinetics. Up until the early 1990's the only pharmacokinetics test data actually utilized was that gained from experimental animals. The data received was therefore used merely in the supplemental interpretation of toxicity tests. More recently, human liver samples have become widely available, thus leading to increased importance of human *in vitro* metabolism testing, in addition to conventional animal testing. Therefore, non-clinical pharmacokinetics testing has now begun contributing to the important task of verifying drug safety in humans. More specifically, the role of this testing now includes: (i) determining the validity of toxicity testing through confirmation of similarities between the metabolisms of experimental animals and humans; and (ii) prediction of side effects (particularly drug interactions) by the simulation of pharmacokinetics in humans. The data from these safety and pharmacokinetics tests are submitted to the regulatory authorities as reference material to be used in applications for drug approval.

A summary of pharmacokinetics testing conducted during the drug development stage is described below.

(1) Pharmacokinetics Testing Using Experimental Animals (*in vivo*)

Pharmacokinetics testing via the administration of radiolabeled compound to experimental animals (usually rats, dogs or monkeys used in general toxicity testing) is conducted to study a compound's absorption, organ distribution and excretion. The objective of this testing is to determine species differences and target organ of toxicity. In addition, this testing seeks to elucidate the structure of metabolites within the plasma, urine and bile, which can be used to screen for the presence of pharmacologically active and toxic metabolites. Since information on metabolites can affect the evaluation results and the design of both toxicity tests and clinical tests, as described in following sections, the rapid determination of metabolite structure is one key to accelerating the speed of drug development. We therefore begin to acquire radiolabeled compound once the number of candidates has been narrowed down to a single compound. We determine the structures of all major metabolites during the period of preparation for pre-clinical testing (period of bulk pharmaceutical manufacturing).

(2) Pharmacokinetics Testing Using Human Samples (*in vitro*)

(i) Comparison of Human and Animal Metabolisms

This *in vitro* testing is conducted in order to compare the metabolism in the human with those of experimental animals (rat, mouse, dog, monkey, rabbit, etc.). A new drug containing a radioactive tracer is added to either liver microsomes or S9, to precipitate an *in vitro* metabolic reaction. The metabolites produced from each biospecimen are then examined and compared using radio–HPLC. This analysis confirms that animal *in vitro* metabolism is similar to animal *in vivo* metabolism, thus allowing us to assume that human *in vitro* metabolism will reflect the results of human clinical testing. We have started routine use of isolated hepatocytes from humans and from experimental animals, which have both recently become available. We have experienced through many new drug compounds under development that in these hepatocytes, conjugation reactions (glucuronic acid conjugation, sulfuric acid conjugation, amino acid conjugation) that do not easily progress in S9 or microsomes can progress well, thus strongly reflecting the *in vivo* metabolic processes.

We conduct all of the aforementioned testing prior to the initiation of pre-clinical toxicity tests, taking advantage of the results in order to select the most appropriate animal species for toxicity testing (possessing a metabolism similar to that of a human). Moreover, in the event that we detect the production of any metabolites that may be toxic or pharmacologically active in the human body, the plasma concentrations of these metabolites are measured through both toxicity tests (toxicokinetics) and clinical tests.

(ii) Evaluation for Drug Interactions

With respect to drug interactions, both of the following scenarios must be evaluated: (A) whether our product affects the kinetics of other drug combinations and induces their side effects; or the converse, (B) whether other drug combinations affect the kinetics of our product, inducing it to produce side effects.

In evaluating the first scenario (A), we measure the capacity of the new drug candidate to inhibit cytochrome P450 (CYP) activity. Cytochrome P450 (CYP) is a metabolic enzyme that participates in the metabolism of many drugs currently on the market. This evaluation measures the CYP activity level in human liver microsomes, using a probe substrate for each CYP isoform to determine how the inhibitory capacity of the candidate compound affects the metabolic reaction rate. We are conducting evaluation testing on 9 CYP isoforms to determine the inhibitory capacities for CYP, based on Standard Operating Procedures (SOP). If a new candidate compound has a low inhibitory capacity for CYP, then it is judged to have a low possibility of interaction with other drugs in clinical applications. However, any level of inhibitory capacity that is recognized for any particular CYP isoform (example: CYP3A4) indicates a risk that the compound's use may produce hazardous drug interactions. Therefore, if used with any other drugs that have narrow safety margins and that are also metabolized by CYP3A4, then strict warnings must be implemented or combined usage should be prohibited.

In evaluating the second scenario (B), we specify particular CYP isoform that contributes to the metabolism of the new drug candidate. Radiolabeled compound is subjected to reaction with human hepatic microsomes, then inhibitors or specific inhibitory antibodies for each CYP isoform are added, in order to determine the degree to which each isoform contributes to the metabolism of the new drug candidate. Any metabolism of the candidate compound by a single

particular CYP isoform (example: CYP2C9) indicates the risk of potentially hazardous drug interactions. Therefore any clinical application must heed strict warnings against combined usage with any other drugs that inhibit CYP2C9.

To determine whether *in vitro* drug interaction test data are of significance in clinical applications, it is necessary to evaluate the properties of the new candidate drug, as well as the properties (i.e., pharmacokinetics and toxicity) of drugs that will be used in combination with the new candidate, in actual clinical applications. Therefore, we have created a drug interaction evaluation system via the following actions: created a list of existing drugs that are frequently combined to treat diseases targeted for new drug development by Sumitomo Pharmaceuticals; conducted broad literature research pertaining to both the side effects and human kinetics data (metabolic enzymes, excretion pathways, pharmacokinetics parameters, etc.) for existing drugs; and lastly, developed a database to facilitate access to the resulting information.

As described above, in the non-clinical evaluation of a new compound, both toxicity testing and pharmacokinetics testing are required constituents of a safety evaluation. Pharmacokinetics data have been acknowledged by regulatory authorities as providing a highly accurate means of extrapolating toxicity test data to humans, by bridging the gap created by the species differences between humans and experimental animals. A variety of guidelines have therefore been set forth with respect to pharmacokinetics (**Table 1**). At the same time, data reliability is also regulated under the Pharmaceutical Affairs Law. These regulations, which are referred to as "Reliability Standards," require that test data be accurate and that the experimental process be fully traceable, with precise preservation of references. In particular, since *in vitro* drug interaction test results are treated as a scientifically valid justification for omitting clinical drug interaction studies, disputes have intensified over the necessity of conducting validation testing using the Reliability Standards, to guarantee enzyme activity measurement systems.[1)]

Table 1 Guidelines related to pharmacokinetics study

Title	Primary Content
"Guidance for Non-clinical Pharmacokinetic Studies" (Ministry of Health and Welfare Japan, 1998)	Preferable package of animal pharmacokinetics studies is documented. Investigation to the difference in metabolism between animals and human is encouraged to contribute to more precise safety evaluation of the drug candidates.
"Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (ICH Harmonised Tripartite Guideline, 1997)	Exposure data in animals should be evaluated prior to human clinical trials. Further information on absorption, distribution, metabolism and excretion in animals should be made available to compare human and animal metabolic pathways. Appropriate information should usually be available by the time the Phase I (Human Pharmacology) studies have been completed.
"Methods of Drug Interaction Studies" (Ministry of Health, Labour and Welfare Japan, 2001)	Investigation to *in vitro* drug-drug interaction studies (e.g., metabolic enzyme inhibition study) prior to clinical trials with multi-drug therapy is recommended.
"Guidance for Industry; Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro*" (Center for Drug Evaluation and Research, USFDA, 1997)	
"Note for Guidance on the Investigation of Drug Interactions" (Committee for Propriety Medicinal Products, European Medicines Agency, 1998)	

Current Status and Future Prognosis for New *in Silico* Research Methodology

In conventional pharmaceutical evaluations, *in vitro* methods are utilized in conjunction with *in vivo* methods. However, in recent years, opportunities have increased for utilizing *in silico* methodologies that employ computer simulation. In this section, we describe the GastroPlus™ software that our company is currently utilizing, as well as other methods of *in silico* modeling (virtual clinical trial). We expect the usage of *in silico* modeling to increase greatly in the near future.

1. *in Silico* Pharmacokinetics Prediction Research

– Predicting Plasma Concentration profile of Oral Agents in the Human Body –

(1) Significance of Predicting Drug Plasma Concentration profile in the Human Body

The plasma concentration of a drug is often the dominant factor affecting its efficacy and side effects. In general, the therapeutic range of plasma concentrations for a particular drug consists of an ineffective zone, an effective zone and a toxic zone (**Fig. 6**). In

order to ensure the safe administration of a drug, the appropriate dosage must be accurately specified prior to the first administration of the drug, in order to ensure that the drug's plasma concentration level remains within the effective zone. Therefore, the accurate prediction of pharmacokinetics within the human body contributes directly to improvement in the success rate for clinical development. Although animal data has been utilized widely as a means of predicting the kinetics of oral agents taken into the human body, this data is not always completely accurate in reflecting the absorption profile of a drug in the human gastrointestinal tract. Thus, this method does not produce highly accuracy predictions. We have therefore introduced the GastroPlus™ software for research aimed at improving the accuracy of predicting drug pharmacokinetics within the human body. Among all of the commercial software that employs a pharmacokinetics approach to simulating drug absorption within the human gastrointestinal tract, GastroPlus™ has demonstrated the greatest accuracy.

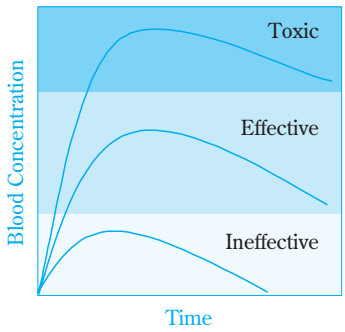


Fig. 6 Therapeutic Range

(2) "GastroPlus™" Simulation Software

From the point at which a drug is orally administered, until it is absorbed, the drug must first dissolve, then transit into the gastrointestinal tract, where it finally permeates into enterocytes. In some cases, drug decomposition occurs within the gastrointestinal tract and in other cases the drug is metabolized within enterocytes. These phenomena occur continuously and simultaneously. GastroPlus™ is a software program that uses a series of mathematical models to express these simultaneous and ongoing phenomena, thus accurately simulating absorption profile.

First of all, the factors relating to the oral absorption of the new drug are measured and input. These factors include "particle size, lipophilicity, pKa, solubility (as affected by pH and bile salts), as well as the human intestinal permeability." GastroPlus™ contains preprogrammed variables for gastrointestinal tract conditions, including pH, volume, blood flow and transit times. GastroPlus™ uses a mathematical model containing these data to create a simulated absorption profile for the new drug. Furthermore, the changes in drug plasma concentrations corresponding to the absorption profile can be simulated through calculations utilizing factors such as the "metabolism rate, distribution volume, plasma protein binding and blood/plasma concentration ratio" (**Fig. 7**).

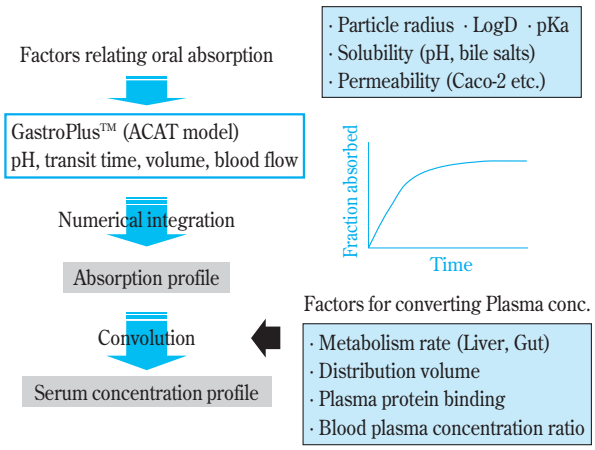


Fig. 7 Flow Chart of Simulation

(3) Verification of Prediction Accuracy

In this section, we introduce an example that uses the dihydropyridine calcium antagonist "Amlodin®," sold by Sumitomo Pharmaceuticals, to demonstrate the verification of GastroPlus™ prediction accuracy. Amlodin® is well-suited for use in verifying prediction accuracy, as abundant human pharmacokinetics data are already available.

All of the aforementioned elements relating to the oral absorption of the drug can be obtained through *in vitro* testing. On the other hand, the factors used to convert these elements to plasma concentrations contain pharmacokinetics parameters that cannot be measured unless the drug is administered intravenously. These parameters include the clearance and the distribution volume. In general, data obtained from separately conducted *in vitro* and *in vivo* animal tests is utilized for these parameters. However, in order to verify the prediction accuracy of GastroPlus™ for absorption profile, we have also included the clearance value and distribution volume as parameters, which have previ-

ously been measured after the intravenous administration of Amlodin® to humans. First, a simulated absorption profile was computed using *in vitro* test data for 5 mg of Amlodin®, administered orally on fasted condition (**Fig. 8**). The fraction absorbed was calculated as approximately 70%. **Fig. 9** depicts the simulation calculated for Amlodin® plasma concentration, obtained from the absorption profile, as well as the actual measured data. Since the simulation is seen to correlate very closely to the actual measurements, we can conclude that the absorption profile in the body has been accurately simulated from the parameters relating to the absorption profile obtained from *in vitro* testing.

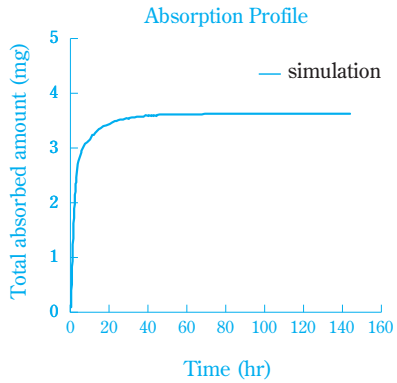


Fig. 8 Absorption Profile of Amlodin (5mg/man)

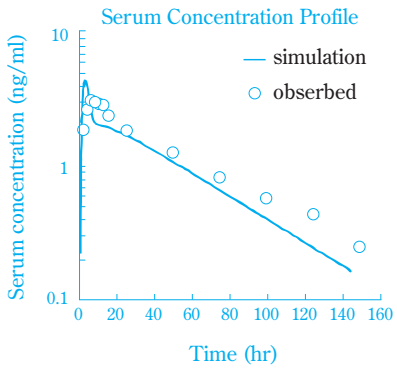


Fig. 9 Serum Concentration Profile of Amlodin (5mg/man)

(4) Application to New Drugs Under Development

As this kind of simulation is conducted prior to clinical testing, the parameters used to calculate plasma concentrations (such as pharmacokinetic parameters within the human body) are not yet available at that time. Therefore, another key to achieving high prediction accuracy for drug plasma concentration profile is ensuring that such parameters are estimated extremely accurately. For pharmacokinetic parameters within the human body, it is necessary to estimate both the distribution volume, which indicates the amount of drug that is transferred to the tissues, as well as the clearance, which indicates the rate at which the drug is eliminated from the body. The rule of thumb that is generally utilized in estimating these values is referred to as "animal scale up." In order to improve the prediction accuracy, we have added some scientific basis to this method of estimation by breaking it down into its constituent parameters, which represent the more detailed elementary processes involved with both clearance and distribution volume. To evaluate each of these elementary processes, we usually employ methods in which *in vitro* tests, which have been appropriately designed to accurately reflect the results of *in vivo* testing, are combined with several types of animal testing. As well, we also conduct examinations using new tools, such as human tissues, including isolated hepatocytes, which have recently become available, in aiming to achieve greater accuracy in the prediction of drug plasma concentration profile.

Furthermore, as human characteristics, such as drug metabolic capacity and stomach pH, vary among individuals, we are also able to simulate the resulting fluctuations in drug plasma concentrations among different individuals. We presently conduct such simulations whenever necessary.

2. More Efficient Development Through *in silico* Modeling

(1) Circumstances Under Which *in silico* Modeling is Utilized

An example showing the use of GastroPlus™ for the *in silico* pharmacokinetics simulation of drug plasma concentrations was described in the previous section. By contrast, *in silico* modeling utilizes these procedures to investigate drug action and behavior (including pharmacokinetics performance) on the human body. Under today's circumstances, in which approximately 50% of all drugs under development are discontinued during the early stages of clinical testing[2], a trend is now being seen among leading US and European pharmaceutical companies, to take advantage of *in silico* modeling (if applied in clinical testing, this is occasionally referred to as a "virtual clinical trial") as a means of improving the success rates for drug development. Since the expenses for clinical testing represent a large proportion of total drug research and development costs, an increase of merely

20% - 30% in the success rate can decrease the overall cost of developing a single registered pharmaceutical product, by approximately $240 million.[3] This is the primary reason why pharmaceutical manufacturers are paying tremendous attention to *in silico* modeling; using it to design more efficient clinical testing procedures and to predict drug side effects prior to actual clinical testing. Currently, many pharmaceutical manufacturers are utilizing *in silico* modeling systems that combine both clinical data and -omics data and are capable of systematically describing the biological control mechanisms for both the healthy condition and the disease condition.

The driving forces behind the recent tremendous strides made in prediction methodologies, are as follows: due to rapid advances in computer technology, software simulation systems are now able to run on inexpensive desktop computers; complex, large-scale biological measurements can now be accurately conducted in terms of quantitative analysis; we have gained a deeper understanding of complex biological systems; and the construction of mathematical models has become much more advanced.[4] Some of the new models simulating drug metabolism in the human body possesses more than 400 variables. This type of advanced model can simulate the results obtained from a continuous 24-hour full testing regimen in a mere 45 minutes.

As described above, the purpose of *in silico* modeling is to integrate biological data (genomics data, physiological data, etc.) within a computer-based platform. *in silico* modeling uses this platform to predict future biological responses under certain dynamic conditions. The employment of *in silico* modeling will allow researchers to deepen their basic understanding of disease, thus enabling them to better answer questions regarding what is happening within the organism and why it is happening - in other words, gaining a better understanding of drug efficacy, toxicity and kinetics. Thus, *in silico* modeling makes possible the prediction of the following:

– Effects of drugs on cells and tissues
– Effects of drugs on the human body during clinical testing

Therefore, *in silico* modeling, with its ability to describe and predict the effects of drugs within the human body, is useful at every stage of drug manufacture, from the developmental stage through to the clinical stage.[5), 6)]

(2) Application of Large-Scale *in silico* Modeling

in silico modeling can be classified into two types, in accordance with the scale.[7] Small-scale *in silico* modeling consists of several parameters and a few mathematical formulae. It is designed to deal with only a specific and limited set of problems. In contrast, large-scale *in silico* modeling is comprised of thousands of parameters and mathematical formulae, designed to describe complex biological processes. In this section, we describe the kinds of benefits that large-scale *in silico* modeling (of sufficient size to be applied to clinical testing) can bring to the drug development process.

(i) Discovery and Pre-Clinical Stage

Application of *in silico* modeling to lead identification can help determine and set the target priorities (targets for drug actions). In conventional *in vitro* systems, for example, cells considered to be of functional significance in the disease process are extracted from the body's control systems. As well, within *in vivo* systems, a disease condition is artificially induced to push the body's control system out of equilibrium. *in silico* modeling allows us to change the target activity while simulating such conditions within the human body, then allowing the prediction of pathways that will induce the strongest clinical effects.

(ii) Clinical Stage

Among all the stages of drug development, the clinical testing stage requires the greatest input of resources. Although *in silico* modeling can be applied to many areas, those models that particularly represent overall body physiology can be utilized to design and optimize clinical testing in the following ways:

– Optimizing the clinical test protocol
– Optimizing the method of drug administration
– Optimizing the timing for sampling
– Optimizing the time required for accomplishing the goals of clinical testing
– Predicting therapeutic effects
– Proposal of drug administration patterns that will achieve the best possible clinical results

Furthermore, it also appears that *in silico* modeling makes it possible to obtain other useful information, such as: for which patient groups a specific drug will be most effective (or least effective); why certain specific reactions occur; and the degree of reaction fluctuation within a patient group.

(3) Examples of Applications for *in silico* Modeling [8), 9), 10)]

The ultimate goal for *in silico* modeling is the development of new drugs solely through the modeling process, without the need to conduct screening or toxicity tests using animals and further, without the need for clinical testing. However, in reality, even venture companies who make *in silico* modeling their core business, have recognized that *in silico* modeling has not yet reached the stage where it is capable of such complete utility.

However, as described above, *in silico* modeling can reduce the time and costs associated with drug development, thus has been attracting attention as one of the most effective means of assisting in the decision-making process for the selection of candidate compounds. Since the results of simulations are not usually released to scientific journals or similar publications, the full extent of success achieved by *in silico* modeling is not well known. However, the utility of *in silico* modeling will be described using the example of Entelos, a leading *in silico* modeling company. Entelos is well recognized as a company that has entered into many new drug research and development partnerships with large US pharmaceutical companies (i.e., Pfizer, Merck).

Entelos focuses upon the variability of the genetic and environmental factors that cause disease. The company believes that for the disease of diabetes, no single individual expresses symptoms that are identical to those of any other individual, thus *in silico* modeling must reflect this fact. Johnson & Johnson (J & J) utilizes PhysioLab technology, developed by Entelos, for screening new drug candidates and for analyzing clinical test data. J & J claims that by gaining a more comprehensive understanding of diabetes and by predicting the manifestation of symptoms in the human body, they can develop more appropriate and feasible remedies (i.e., combinations of drugs and equipment). Regulatory authorities, such as the FDA, are also paying close attention to *in silico* modeling as a means of achieving the following efforts: increasing the safety of existing drugs; addressing the shortcomings of conventional methods of evaluating efficacy; and accelerating drug development.[11), 12)] As described above, *in silico* modeling technology is expected to have a huge impact, not only on pharmacokinetics, but also on all aspects of future drug research. Therefore, it will become necessary to apply *in silico* modeling to the entire drug development process.

Conclusion

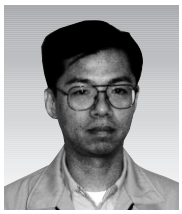
In recent years, the terms “made-to-order medical care” and “tailor-made medical care” have become popular, even throughout society in general. As indicated by these terms, much change is now being demanded from the medical system, from the conventional “mass therapeutics,” toward a more personalized medical care system that is tailored to the drug reactions and hereditary body characteristics of each individual patient. In addition, increasing demand is also being seen for “evidence-based medicine.” Furthermore, as the human genome project progresses, new challenges have emerged, such as drug reaction genomics and the creation of genomic drugs. The regulatory authorities in charge of new drug approvals are also expressing great interest in the current progress. Thus, we believe that our mission in this area, which has shown increasingly drastic change since the beginning of the 21st century, is to further improve the “Sumitomo pharmacokinetics research strategy” through the appropriate implementation of the necessary technologies and procedures, with a constant awareness of new trends in global drug development and pharmacokinetics research.

References

1) R. L. Walsky and R. S. Obach “Validated assays for human cytochrome P450 activities”, Drug Metab Dispos, 32, 647 (2004)
2) D. Polidori and J. Trimmer, “Bringing advanced therapies to market faster; a role for biosimulation?”, Diabetes Voice, 48 (2), 28 (2003)
3) Tufts Center for the Study of Drug Development, Impact Report, 4 (5), (2003)
4) C. M. Henry, “Systems Biology”, Chemical & Engineering News, 81(20), 45 (2003)
5) S. Michelson, “Assessing the Impact of Predictive Biosimulation on Drug Discovery and Development”, J. of Bioinfo. And Comp. Biology, 1, 169 (2003)
6) Entelos, Inc., “Assessing the Impact of Predictive Biosimulation on Pharma R&D”, http://www.entelos.com
7) J. Musante, A. Lewis and K Hall, “Small- and large-scale biosimulation applied to drug discovery and development”, Drug Discovery Today, 7, S192 (2002)
8) M. Goldman, “A Virtual Pharmacopeia”, Bio IT

World, November (2002) http://www.bio-itworld.com/archive/111202/virtual.html
9) M. Uehling, "Model Patient", Bio IT World, December (2003)
10) R. C. Willis, "Virtual Patient", Modern Drug Discovery, 35 (2003)
11) C. Peck and D. Rubin, "Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval", Clin. Pharmacol. Ther., 73, 481 (2003)
12) Food and Drug Administration, "Innovation and Stagnation", March (2003)

PROFILE



Kimihiko Sato
Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Senior Research Associate

Masashi Yabuki
Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Senior Research Associate
Ph. D.

Takao Watanabe
Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Research Associate

Setsuko Komuro
Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Group Manager
Ph. D.

Kazuhiko Nishioka
Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Senior Research Associate